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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/889,756 | 12/31/2001 | Joelle Thonnard | BM45353 | 8852 |

25308 7590 09/30/2003

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EXAMINER

BASKAR, PADMAVATHI

| ART UNIT | PAPER NUMBER |
|----------|--------------|
|----------|--------------|

1645

DATE MAILED: 09/30/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/889,756

Applicant(s)

THONNARD, JOELLE

Examiner

Padmavathi v Baskar

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19,21,24,26,27,30,35,36,38 and 42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19,21,24,26,27,30,35,36,38 and 42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

1. Applicant's response to restriction in Paper No.10 (6/6/03) is acknowledged. Claims 19-42 are pending in the application.

Election

2. Applicant's election Group I, claims 19, 21, 24, 26, 27, 30, 35, 36, 38 and 42 with respect to SEQID.NO: 2 without traverse (6/6/03) in Paper # 10 is acknowledged. Claims 20, 22-23, 25, 28-29, 31-34, 37, and 39-41 have been canceled. Claims 19, 35 and 36 have been amended, Claims 19, 21, 24, 26, 27, 30, 35, 36, 38 and 42 are under examination.

Priority

This application is a national stage entry of PCT/EP00/00425(01/19/2000)

Which claims priority to

| Priority# | Date | Country |
|-----------|------------|----------------|
| 9902069.5 | 01/29/1999 | UNITED KINGDOM |
| 9901462.3 | 01/22/1999 | UNITED KINGDOM |

The examiner has reviewed the foreign document 9902069.5 and finds support for the claimed invention with respect to SEQ.ID.NO: 2 containing 412 amino acids. Therefore, this application gets priority as of filing date 1 /29/1999 of foreign document U.K. 9902069.5 However; the examiner could not locate the other foreign document U.K. 9901462.3 in the application. Applicant is advised to send the foreign document U.K. 9901462.3 in order to get the priority date as of 1/22/1999.

Drawings

3. The drawings are objected to by the draftsman under 37 C.F.R. 1.84 or 1.152. See attached PTO-948 for details.

Information Disclosure Statement

4. The Information Disclosure Statement filed on 2/20/03 (Paper # 9) is acknowledged and a signed copy is attached in this application.

Specification - Informalities

5. Applicant should follow the direction or order or arrangement in framing the specification as provided in 37 CFR 1.77(b) since this is a utility application filed in USA. The specification should include all the sections in order. For example: Claims should begin with "I claim" or "we claim" or "What is claimed is". The specification does not refer to any drawings and no Brief Description of Drawings are present in the application

It is noted that Abstract of the Disclosure is missing. If applicant desires to include the abstract from PCT/EP00/00425, a copy of the abstract will be inserted in to the specification.

There are no line numbers in the specification pages.

Claim Rejections - 35 USC 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 19, 21, 24, 26, 30, 35, 36, 38 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at

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Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

The specification describes the recombinant polypeptide BASB055, SEQ ID NO: 2, from *Neisseria meningitidis* comprising 412 amino acids with a molecular weight of 50kD. The actual biological function of the polypeptide, SEQ ID NO: 2 is not set forth in the specification.

Applicants broadly describe the fragments of SEQ.ID.NO: 2 obtained by embracing any substitution, insertion or deletion of amino acid throughout the entire stretch of polypeptide by use of language in which a fragment sequence of 15 contiguous amino acids or 20 contiguous amino acids of SEQ.ID.NO: 2. None of these fragments meets the written description provision of 35 U.S.C. 112, first paragraph. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116.).

The specification fails to teach a single fragment of a polypeptide sequence of SEQ ID NO: 2 and it is noted that the claimed polypeptides do not exist as an invention independent of their function in a putative outer membrane polypeptide. The actual structure or other relevant identifying characteristics of each fragment having the claimed properties of the polypeptide can only be determined empirically by actually making every amino acid which can result in fragments with 15 or 20 amino acids and testing each to determine whether it is a polypeptide having the particularly disclosed properties of an BASB053 polypeptide.

There must be some nexus between the structure of the polypeptide fragments and the function of that fragment. The specification fails to teach the structure or relevant identifying

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characteristics of a representative number of species of a representative number of polypeptides, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. With the exception of an isolated polypeptide comprising SEQ ID NO: 2, fragments comprising 15 or 20 amino acids the skilled artisan cannot envision the contemplated sequences by the detailed chemical structure of the claimed fragments regardless of the complexity or simplicity of the art. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc V Chuaai Pharmaceutical Co Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

8. Claims 19, 21, 24, 26, 30, 35, 36, 38 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence SEQ ID NO: 2 and a fusion protein comprising the amino acid sequence as set forth in SEQ.ID.NO: 2 and an heterologous amino acid sequence, the specification does not reasonably provide enablement for any immunogenic polypeptide comprising a fragment sequence of at least 15 or 20 amino acids that matches contiguous segment of SEQ.ID.NO: 2 or vaccines comprising SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Instant claims are evaluated for enablement using Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The specification fails to indicate the biological activity of fragment sequence of 15 or 20 contiguous amino acids of SEQ.ID.NO: 2. The specification is not enabled for any immunogenic fragment sequence of at least 15 or 20 amino acids that matches contiguous segment of SEQ.ID.NO: 2, because the specification fails to teach how to make and use fragments thereof that have an unknown and uncharacterized function; the specification fails to teach what are the critical residues that can be modified and still achieve a fragment with any functional activity or any fragments with characteristics for *Neisseria meningitidis* and the art teaches that polypeptides with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of the function of claimed fragments.

The specification fails to provide a written description of any fragment sequence of at least 15 or 20 amino acids of SEQ.ID.NO: 2. The specification fails to teach the critical polypeptide residues involved in the function of the polypeptide SEQ ID NO: 2, such that the skilled artisan is provided guidance to test, screen or make fragments of SEQ ID NO: 2 using conventional technology which allow for any use. The specification fails to teach to what extent one could alter SEQ ID NO: 2 that would not lead to unpredictable results regarding the functional activity of the fragments. Moreover, polypeptide chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE

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HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6): The art specifically teaches that even a single amino acid change in a polypeptide leads to unpredictable changes in the biological activity of the polypeptide. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the polypeptide (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a polypeptide. Polypeptides with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products polypeptides that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. Since, the specification lacks a written description of any immunogenic fragment sequence of at least 15 or 20 SEQ.ID.NO: 2 it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed polypeptide fragments of SEQ ID NO: 2 as well as how to use the polypeptide fragments, one of skill in the art would be unable to produce these polypeptide fragments encompassed by the instant claims.

Claim Rejections - 35 USC 112, second paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 19, 21, 24, 26, 27, 30, 35, 36, 38 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is vague and not clear whether the immune response induced by the immunogenic fragment has the ability to bind to an antibody raised against full-length protein. It is suggested that this claim to be amended to recite " An isolated polypeptide ----, wherein the immunogenic fragment when administered----- -- immune response that recognizes the isolated polypeptide SEQ ID NO: 2.

Claim 42 is rejected as being vague in reciting " wherein the immune response that recognizes an antigen" It is not clear how an immune response recognizes an antigen. Does applicant intend to mean wherein the isolated polypeptide according to (a) induces an antibody that recognizes an antigen having molecular weight of 50kD as determined by SDS-PAGE? Or something else?

Claim Rejections - 35 USC 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 19, 21, 24, 26, 30, 36, 38 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Martin et al 1997 (J.Ex.Med. Volume 185, Number 7, April 7, 1997 1173-1184).

Claims are directed to an isolated polypeptide and immunogenic composition comprising an amino acid sequence SEQ.ID.NO: 2, a fragment sequence of at least contiguous 15 or 20 amino acids of SEQ.ID.NO: 2, fusion protein comprising said peptide etc.

Martin et al disclose an isolated polypeptide, outer membrane protein from whole cell lysate of OM preparations from various clinical isolated including nine meningococcal strains two of serogroup A (604A and Z4063), one of serogroup B (608B [B: 2a:P1.2: L3]), two of serogroup C (2241C and 59C), one of serogroup 29-E, one of serogroup W-135, one of serogroup Y (SLATY) and one of serogroup Z (SLATZ) (page 1174, under materials and method, antigens). Monoclonal antibodies were generated by immunizing mice with different combinations of OM preparations (page 1176, left column, 2nd paragraph) indicating that the preparation is immunogenic and thus read on immunogenic composition as well as method of inducing an immune response of the claimed invention. Applicant's use of the open-ended term "comprising" in the claims fails to exclude unrecited steps or ingredients and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. Whole cell lysates prepared in buffer (pharmaceutical carrier) from *Neisseria meningitidis* inherently comprise the amino acid sequence as set forth in the SEQ.ID.NO: 2 and several *Neisseria meningitidis* antigens and thus read on fusion proteins. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). In the absence

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of evidence to the contrary the disclosed prior art protein and the claimed isolated polypeptide comprising SEQ.ID.NO: 2 are the same. Since the Office does not have the facilities for examining and comparing applicants' claimed isolated polypeptide comprising SEQ.ID.NO: 2, with the polypeptide of prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. Therefore, the prior art anticipated the claimed invention.

13. Claims 19, 24, 26, 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Pan et al (Mol.Microbiol, 11; 769-775, 1994 and Accession number p 43505)

The claims are described supra.

Pan et al disclose an isolated polypeptide comprising 15 or 20 contiguous amino acids of SEQ.ID.NO: 2 (see the Accession number p 43505 sequence alignment with the claimed polypeptide). The disclosed polypeptide 96% identical with the claimed polypeptide SEQ.ID.NO: 2. Since this polypeptide contains more than 20 amino acids, it induces an immune response as the state of the art in immunology teaches a peptide that contains five amino acids would induce an immune response. In the absence of evidence to the contrary the disclosed prior art polypeptide anticipated the claimed polypeptide and fragments that comprise 15 or 20 amino acids. Therefore, the prior art anticipated the claimed invention.

14. Claim 27 is free of prior art.

Status of Claims

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D.

9/26/03


LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
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